ORIGINAL ARTICLE

Outcomes of Childhood Asthma and Wheezy Bronchitis
A 50-Year Cohort Study

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Abstract

Rationale: Cohort studies suggest that airflow obstruction is established early in life, manifests as childhood asthma and wheezy bronchitis, and continues into early adulthood. Although an association between childhood asthma and chronic obstructive pulmonary disease (COPD) in later life has been demonstrated, it is unclear if childhood wheezy bronchitis is associated with COPD.

Objectives: To investigate whether childhood wheezy bronchitis increases the risk of COPD in the seventh decade.

Methods: A cohort of children recruited in 1964 at age 10 to 15 years, which was followed up in 1989, 1995, and 2001, was followed up again in 2014 when at age 60 to 65 years. Discrete time-to-event and linear mixed effects models were used.

Measurements and Main Results: FEV_1 and FVC were measured. COPD was defined as post-bronchodilator $FEV_1/FVC < 0.7$. Childhood wheezing phenotype was related to 1989, 1995, 2001, and 2014 spirometry data. Three hundred thirty subjects, mean age 61 years, were followed up: 38 with childhood asthma; 53 with childhood wheezy bronchitis; and 239 control subjects (of whom 57 developed adulthood-onset wheeze between ages 16 and 46 yr). In adjusted multivariate analyses, childhood asthma was associated with an increased risk of COPD (odds ratio, 6.37; 95% confidence interval, 3.73–10.94), as was childhood wheezy bronchitis (odd ratio 1.81; 95% confidence interval, 1.12–2.91). The COPD risk increased with childhood asthma, and wheezy bronchitis was associated with reduced FEV_1 that was evident by the fifth decade and not an accelerated rate of FEV_1 decline. In contrast, adulthood-onset wheeze was associated with accelerated FEV_1 decline.

Conclusions: Childhood wheezy bronchitis and asthma are associated with an increased risk of COPD and reduced ventilatory function.

Keywords: childhood wheezing phenotypes; asthma; chronic obstructive pulmonary disease; pulmonary function decline

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide (1). In the United Kingdom, approximately 900,000 people have diagnosed COPD, with an estimated additional 2 million people being undiagnosed (2). COPD is the fifth leading cause of death, accounting for approximately 30,000 deaths annually (3, 4), and is a leading cause of emergency hospitalization (5). In developed countries, cigarette smoking is the major risk factor for COPD; however, additional factors are important because the population attributable fraction for smoking is <80% (6), and only a minority (10–20%) of smokers develop clinically significant disease (7).

Many preschool children (20% by 6 yr) develop wheezing symptoms (wheezy bronchitis/virus-associated wheeze [WB/VAW]) during episodes of viral respiratory tract infection, but they are asymptomatic thereafter (8). Epidemiological findings suggest that childhood WB/VAW and COPD may be closely associated (9), because both are the consequence of an underlying abnormality of airway development characterized by reduced ventilatory function in early life and possibly accelerated ventilatory function decline in later life. Studies have reported associations between childhood records of lower respiratory tract infection and

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At a Glance Commentary

Scientific Knowledge on the Subject: The outcome in later life of childhood wheezing illness confined to viral respiratory tract infections (wheezy bronchitis/viral associated wheeze [WB/VAW]) is unknown. Recent birth cohort studies suggest tracking of suboptimal lung function from birth is associated with WB/VAW and predict WB/VAW to be associated with an increased risk of chronic obstructive pulmonary disease (COPD) in later life. A previous longitudinal study spanning 50 years demonstrated that childhood asthma, but not WB/VAW, was associated with COPD in later life.

What This Study Adds to the Field: This 50-year cohort study has followed children to the oldest age of any of the existing cohorts to date. This study has shown for the first time that childhood WB/VAW is associated with an increased risk of COPD and reduced lung function in the seventh decade. This finding should lead to a re-evaluation of the advice given to children with WB/VAW and their parents, of the increased risk of COPD and the need to avoid additional risk factors such as smoking. Later-life monitoring of ventilatory function may be deemed appropriate.

reduced FEV_1 or COPD during adulthood (10, 11). Birth cohort studies have demonstrated tracking of ventilatory function with reduced neonatal/infant ventilatory function being associated with WB/VAW, childhood asthma (CA), reduced FEV_1, and airflow obstruction up to age 22 years (8, 12–14). Addressing the issue of whether WB/VAW increases COPD risk requires a prospective study that relates childhood WB/VAW to ventilatory function in middle/old age. The Melbourne Asthma Study (MAS) recruited 484 children aged 7 years based on wheezing/asthma status in 1964 and measured ventilatory function at age 50 years. Although CA was associated with COPD, WB/VAW was not (15, 16).

The Aberdeen WHEASE (What Happens Eventually to Asthmatic children: Sociologically and Epidemiologically) cohort of children recruited in 1964 is similarly placed to investigate whether WB/VAW increases the risk of COPD. Follow-up of this cohort in 2001, when the subjects were aged 47 to 52 years, demonstrated that childhood WB/VAW was associated with an increased rate of FEV_1 decline that, if sustained, could result in COPD (17–20). We report the 50-year follow-up of the WHEASE cohort to test the hypothesis that childhood WB/VAW increases the risk of COPD in the seventh decade of life. The study was also able to investigate the effects of CA and adult-onset wheeze (AOW) on the risk of COPD.

Methods

WHEASE Cohort

In 1964, a random 20% sample of Aberdeen schoolchildren aged 10 to 15 years (n = 2511), reported that 288 children had "ever had a wheezy chest" (18). After a pediatrician reviewed primary and secondary care medical records, and conducted a face-to-face clinical assessment, 121 children were classified as having CA (recurrent dyspnea of an obstructive type without demonstrable cause), and 167 were classified as having WB (wheeze only in the presence of upper respiratory tract infection). The remaining 2223 children had no respiratory symptoms (control subjects). Childhood spirometry was recorded for subjects with asthma and WB/VAW, but was not recorded in control subjects. In 1989, when the subjects were aged 35 to 40 years, ventilatory function was measured in 72 subjects with CA, 107 with WB, and a random sample of 93 control subjects (20). In 1995, at age 41 to 46 years, in a cluster case–control study, ventilatory function was measured in 212 control subjects and 100 subjects who had developed wheeze between 16 and 46 years; these subjects were classified as having AOW (17). In 2001, at age 47 to 52 years, subjects from WHEASE-1989 and -1995 were contacted, and ventilatory function was measured in 46 subjects with CA, 65 subjects with WB/VAW, 57 subjects with AOW, and 213 control subjects (19).

In 2014, all participants of WHEASE-1989, -1995, and -2001 were invited to participate in the fourth follow-up.

Assessments and Outcomes

Assessments were identical to WHEASE-2001 (19). A researcher administered the same modified version of the Medical Research Council questionnaire (21) to assess respiratory health, medication, and smoking status. Spirometry was performed according to American Thoracic Society (ATS)/European Respiratory Society (ERS) standards (22) using a Vitalograph Compact II spirometer (Vitalograph, Buckingham, United Kingdom). Spirometry was performed before and 15 minutes after administration of 400-μg albuterol, and the following parameters were recorded: FEV_1, FVC, and forced expiratory flow at 25% to 75% of FVC ($FEF_{25–75\%}$). The study was approved by the North of Scotland Research Ethics Service (13/NS/0038), and participants provided written informed consent.

Statistical Analysis

The primary outcome was COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease (post-bronchodilator $FEV_1/FVC < 0.7$) (23). Analyses were repeated using an alternative definition (post-bronchodilator FEV_1/FVC less than the lower 95% confidence limit of the internationally agreed predictive equations for normality (LLN)] (22, 24). Pediatric spirometry was adjusted for sex, age, and height referenced to a modern standard (25). Adult spirometric indexes were expressed as the percent predicted as defined by the ERS Global Lung Function Initiative 2012 (24). The primary explanatory variable of interest was the original 1964 childhood wheeze category (i.e., subjects with CA, subjects with WB/VAW, and control subjects) (18). Additional analyses used the WHEASE-2001 categories: subjects with CA; subjects with WB/VAW; control subjects; and subjects with AOW, which included childhood control subjects who developed wheeze between 16 and 46 years. The Scottish Index of Multiple Deprivation (SIMD) (26) quintile scores were used as the metric of socioeconomic status (SES). SIMD is an area-based measure of deprivation based on residential postal code, with the first quintile being the most deprived.

Univariate comparisons between WHEASE-2014 participants stratified by wheezing category used the χ^2 test, Student's *t* test, or analysis of variance,

using Bonferroni adjusted *P* values for between-group differences. Logistic regression was used to relate COPD status at WHEASE-2014 with childhood wheezing phenotype with adjustment for sex, age in 2014, smoking history, and SES. Two methods (27) were used to relate childhood wheezing phenotype to all ventilatory function data collected during WHEASE-1989, -1995, -2001, and -2014. A discrete time to event (COPD) model was used to assess differences between groups, with adjustment for sex, age, smoking history, and SES. Linear mixed effect models were used to analyze repeated FEV_1 over time. All participants were included, and any missing FEV_1 data were assumed to be missing at random. The model was fitted with unstructured covariance to account for the correlated measurements (within a person). The models were adjusted for age in 1989, sex, smoking, height, and SES. Time was entered into the model taking the values of 0, 6, 12, and 25 years to represent assessments made in 1989, 1995, 2001, and 2014. Inclusion of an interaction term for time and wheezing group allowed the production of estimates of change in FEV_1 between groups. Analyses were performed using SPSS (version 22.0; IBM, Armonk, New York) and SAS (version 9.3; SAS Institute Inc., Cary, NC).

Sample Size

We estimated that 80% of the 381 WHEASE-2001 (19) participants would participate in WHEASE-2014. Based on WHEASE-2001, with 304 participants (52 subjects with WB/VAW, 37 subjects with CA, and 215 control subjects), and a 12% prevalence of COPD in control subjects ($\alpha = 0.05$), the study would have 80% power to detect a 2.3-fold change in COPD risk associated with WB/VAW (i.e., control subjects 12%, subjects with WB/VAW 28%).

Results

Three hundred thirty people with a mean ± SD age 60.7 ± 1.5 years participated in WHEASE-2014. Table 1 compares details of those who did or did not take part; nonparticipants were more likely to have a history of smoking. Figure 1 summarizes the participant details throughout the 50 years of this study. Of the 330 participants, 262 had also participated in WHEASE-2001, and the remaining 68 participated in WHEASE-1989 and/or -1995. Based on the original 1964 classification, 38 of WHEASE-2014 participants had had CA, 53 participants had WB/VAW, and 239 were control subjects; using the WHEASE-2001 classification, there were 38 subjects with CA, 53 subjects with WB/VAW, 57 subjects with AOW, and 182 control subjects. Participant characteristics as defined by the 1964 and 2001 wheezing categories are presented in Table 2. Compared with control subjects, those with CA and WB/VAW were more likely to be men ($P = 0.03$ and $P = 0.023$, respectively), those with WB/VAW were from less deprived areas ($P = 0.013$), and subjects with AOW were from more deprived areas ($P = 0.013$). Also, compared with controls, participants with WB/VAW were more likely to have been diagnosed with asthma ($P = 0.023$), whereas subjects with AOW were more likely to have been diagnosed with COPD ($P < 0.001$) or asthma ($P < 0.001$).

Table 1. Details of Participants Who Did or Did Not Take Part in WHEASE 2014

	Nonparticipants (*n = 253*)	Participants (*n = 330*)
Sex, male, n (%)	122 (48.2)	171 (51.8)
Age, yr, mean (SD)	60.8 (1.4)	60.7 (1.5)
Ever smoker, n (%)	158 (63.7)	168 (50.9)*
Wheeze category (based on 2001)		
Childhood asthma, n (%)	34 (13.5)	38 (11.5)
Childhood wheezy bronchitis, n (%)	53 (21.0)	53 (16.1)
Adult-onset wheeze, n (%)	40 (15.9)	57 (17.3)
Control, n (%)	125 (49.6)	182 (55.2)

Definition of abbreviation: WHEASE = What Happens Eventually to Asthmatic children: Sociologically and Epidemiologically.
Smoking and wheeze category data missing for 5 and 1 nonparticipants, respectively.
*$P = 0.002$.

The mean ± SD percentage predicted FEV_1/FVC in childhood (mean age, 12.3 yr) was 89% (19) for the 35 subjects with CA and 100% (8) for 43 subjects with WB/VAW, ($P = 0.001$), and the corresponding mean percent predicted FEV_1 values were 90 (21) and 101 (13) ($P = 0.007$). After adjustment for sex and height, children with CA had a mean reduction in the FEV_1/FVC ratio of 0.08 (95% confidence interval [CI], 0.04–0.11) compared with WB/VAW ($P < 0.001$), and for FEV_1, the mean reduction was 267 ml (range, 0–536) ($P = 0.052$).

Childhood Wheezing Phenotype and COPD Status at 60 to 65 Years

COPD status and ventilatory function at age 60 to 65 years are shown in Table 3. In univariate analyses, compared with control subjects, adults with CA had reduced FEV_1, FVC, $FEF_{25–75\%}$, FEV_1/FVC, and were more likely to have COPD at ages 60 to 65 years when defined as FEV_1/FVC <0.7 or less than LLN (Bonferroni adjusted $P <$ 0.001–0.012). Compared with controls, subjects with AOW, as defined in WHEASE-2001, had reduced FEV_1/FVC (Bonferroni adjusted $P = 0.045$).

The results of multivariate analysis relating childhood wheezing phenotype to COPD status at age 60 to 65 years are presented in Table 4. CA was associated with COPD when expressed as FEV_1/FVC <0.7 or less than LLN, but WB/VAW was not. AOW was associated with COPD when defined as less than LLN ($P = 0.05$). A history of ever smoking was associated with COPD, with odds ratios of typically 3.0 to 3.5; sex and SES were not associated with COPD.

Childhood Wheezing Phenotype and All WHEASE Ventilatory Function Data 35 to 65 Years

The 1964 and 2001 wheeze groupings were related to spirometry data collected in WHEASE-1989, -1995, -2001, and -2014. The results of the time-to-event analysis are presented in Table 5. CA was associated with COPD, which was defined as FEV_1/FVC <0.7 or less than LLN ($P < 0.001$). Based on the 1964 classification, WB/VAW was associated with COPD, which was defined as FEV_1/FVC <0.7 ($P = 0.034$). Repeating the analysis using the 2001 classification demonstrated that WB/VAW was associated with COPD when defined as FEV_1/FVC <0.7 ($P = 0.015$). AOW was

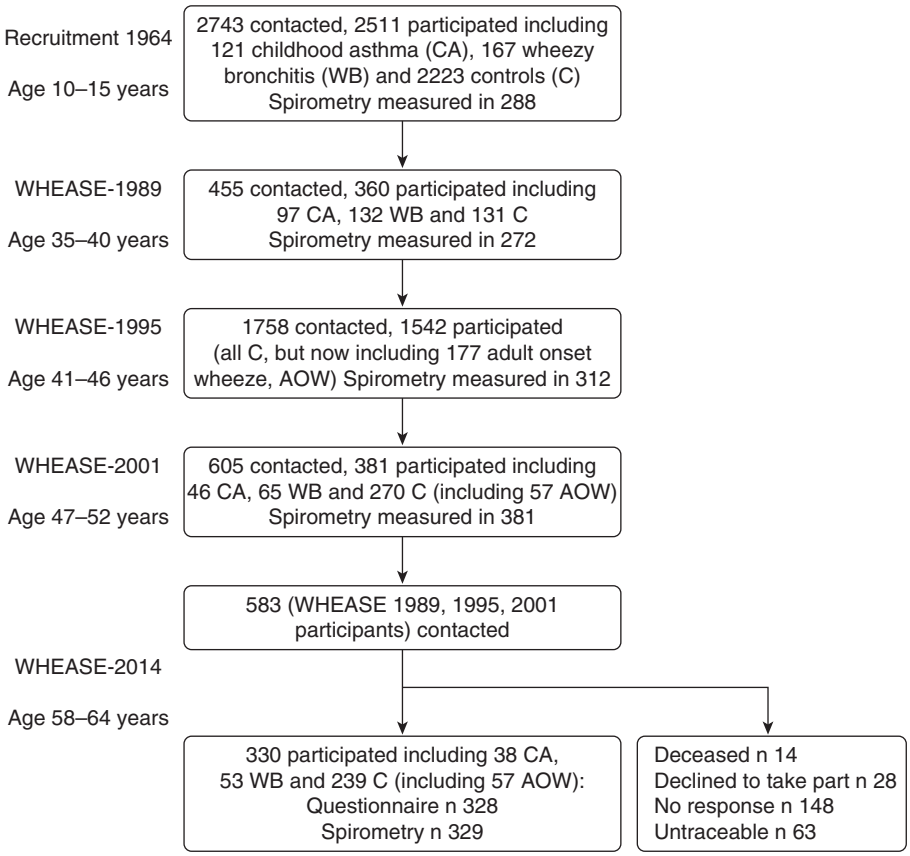

Figure 1. Consolidated Standards of Reporting Trials–style diagram showing the number of individuals invited to participate and the number of participants, including the number in whom lung function was available and the number in each of the wheezing categories.

also associated with COPD when defined as FEV_1/FVC less than LLN ($P = 0.019$).

The results of the linear mixed effects modeling to assess trends in FEV_1 between 1989 and 2014 are presented in Table 6. For those with no wheeze in childhood (i.e., childhood control subjects), the average annual decline in FEV_1 was 34 ml (95% CI, 32–37), and for those with no wheeze reported in childhood or adulthood, the average decline was 33 ml/annum (95% CI, 30–36). Based on the 1964 wheeze phenotypes, compared with control subjects, the mean FEV_1 of participants with CA was 560 ml lower (95% CI 400–720), and the mean FEV_1 of subjects with WB/VAW was 190 ml lower (95% CI, 50–320). However, the rate of FEV_1 decline did not differ between the 1964 wheeze groups.

Repeating this model to include subjects with AOW demonstrated similar associations with those with CA and WB/VAW as previously described. However, compared with control subjects, the FEV_1 of subjects with AOW was no different ($P = 0.573$), but the rate of FEV_1 decline was greater by 9 ml/yr (95% CI, 2–16; $P = 0.008$).

Discussion

For the first time, we demonstrated in a prospective longitudinal study that children with a history of WB/VAW are more likely to develop COPD from the fifth decade onwards. This is likely because of the tracking of reduced FEV_1, which is evident by the fifth decade, and not the increased rate of FEV_1 decline. Although childhood wheezy bronchitis was not associated with COPD when related to ventilatory function data collected at WHEASE-2014 (ages 60–65 yr), an association was evident when related to ventilatory function data collected during the four phases of WHEASE follow-up (ages 35–65 yr), which afforded greater power. Children with asthma already had obstructive spirometry compared with WB/VAW by the age of 10 to 15 years, and were also more likely to develop COPD from the fourth decade onwards. However, this was not a consequence of an increased rate of FEV_1 decline, but was due to preservation of reduced FEV_1 from childhood. A further novel finding was that adults who developed wheezing illness between the ages of 16 and 46 years were at increased risk of COPD from the fifth decade onward because of the increased rate of FEV_1 decline.

The analysis and present findings from the fourth WHEASE follow-up differed from previous studies because COPD as defined by the FEV_1/FVC ratio was the primary outcome; previous WHEASE studies reported FEV_1 and rate of FEV_1 decline as outcomes. Furthermore, this was the first time that all spirometry data from all subjects in all phases of WHEASE follow-up from 1989 to 2014 were included in single models. WHEASE-1989 (20) reported that at ages 35 to 40 years, compared with controls, the percent of predicted FEV_1 of CA (but not WB/VAW) was reduced. In the present study, with the greater power afforded by the analysis of all the data collected in the four follow-up phases of WHEASE (ages 35–65 yr), the FEV_1 of subjects with CA and WB/VAW was significantly reduced compared with control subjects. WHEASE-2001 (19) reported FEV_1 differences between control subjects and subjects with CA (510 ml) and subjects with WB/VAW (180 ml) that were very similar to those we reported of 560 and 200 ml, respectively. Consistent with the difference in adult FEV_1 between CA and WB/VAW, we reported a mean difference in FEV_1 of 267 ml at age 12 years between these groups. In the present study, we reported no differences in the rate of FEV_1 decline among subjects with CA, subjects with WB/VAW, and control subjects, whereas in WHEASE-2001, between 1989 and 2001, the rate of FEV_1 decline of subjects with CA (65 ml/yr) and subjects with WB/VAW (65 ml/yr) was greater than that of control subjects (15 ml/yr). This disparity probably reflects the 2001 analysis being restricted to subjects with paired 1989 and 2001 data, such that only 66 control subjects were included; the present analysis included data from 239 control subjects spanning from 1989 and 1995 to 2014.

Although asthma in early adulthood has been linked to lung function in later life (28), WHEASE is one of a handful of cohort

Table 2. Characteristics of 330* WHEASE 2014 Participants by 1964 and 2001 Wheezing Phenotype Categories

		1964 Definitions			2001 Definitions (Including AOW)	
	Total (*n* = 330)	CA† (*n* = 38)	WB/VAW‡ (*n* = 53)	Controls§ (*n* = 239)	AOW (*n* = 57)	Controls‖ (*n* = 182)
Male, n (%)	171 (51.8)	25 (65.8)	34 (64.2)	112 (46.9)¶	31 (54.4)	81 (44.5)¶
Age, yr, mean (SD)	60.7 (1.5)	60.6 (1.5)	60.9 (1.6)	60.6 (1.5)	60.9 (1.5)	60.5 (1.5)
BMI, kg/m^2, mean (SD)	28.8 (5.8)	30.4 (7.9)	29.6 (5.4)	28.4 (5.5)	29.3 (6.39)	28.2 (5.19)
Smoking ever, n (%)	168 (50.9)	20 (52.6)	23 (43.4)	125 (52.3)	35 (61.4)	90 (49.5)
SIMD quintile, median (IQR)	4 (3–5)	4.5 (3–5)	5 (3–5)	4 (2–5)¶	4 (2–5)	4 (2.5–5)¶
Dyspnea (MRC score ⩾1), n (%)	76 (26.8)	11 (37.9)	12 (26.1)	53 (25.4)	18 (39.1)	35 (21.5)
Chesty cough most days, n (%)	46 (14.0)	8 (21.1)	6 (11.3)	32 (13.5)	13 (22.8)	19 (10.6)
Phlegm most days, n (%)	47 (14.3)	11 (28.9)	6 (11.3)	30 (12.7)**	12 (21.1)	18 (10.0)¶
Wheeze last 12 mo, n (%)	69 (21.0)	20 (52.6)	8 (15.1)	41 (17.2)**	22 (38.6)	19 (10.5)
Asthma diagnosis, n (%)	77 (23.4)	31 (81.6)	11 (20.8)	35 (14.7)††	24 (42.1)	11 (6.1)††
COPD diagnosis, n (%)	18 (5.5)	3 (7.9)	0 (0.0)	15 (6.3)	10 (17.5)	5 (2.8)††
Inhalers prescribed, n (%)	70 (21.3)	27 (71.1)	5 (9.4)	38 (16.0)††	20 (35.1)	18 (9.9)††

Definition of abbreviations: AOW = adult-onset wheeze; BMI = body mass index; CA = childhood asthma; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; MRC = Medical Research Council; SIMD = Scottish Index of Multiple Deprivation; WB/VBW = wheezy bronchitis/virus-associated wheeze; WHEASE = What Happens Eventually to Asthmatic children: Sociologically and Epidemiologically.
*Questionnaire data in 328 subjects and physiological measurements in 329 subjects.
†Childhood asthma.
‡Childhood WB/VAW.
§Childhood controls.
‖Adult controls. In these columns, the individuals with AOW who were defined as controls in 1964 are compared with subjects who never developed respiratory symptoms.
¶$P < 0.02$ for differences across childhood groups by one-way analysis of variance and χ^2 tests.
**$P < 0.03$ for differences across childhood groups by χ^2 test.
††$P < 0.001$ for differences across childhood groups by χ^2 test.

studies able to relate CA and WB/VAW to COPD in middle/old age. MAS recruited 484 children aged 7 years in 1964, followed them up every 7 years, and recently reported follow-up at mean age 51.4 years. The present study confirms the finding by MAS (16) that CA is associated with an increased risk of COPD at age 51 years, and that there is no difference in the rate of FEV_1 decline of CA, WB/VAW, and in control subjects in adulthood. We also replicated the MAS observation that the FEV_1 difference between CA and WB/VAW is established in childhood. We were able to extend the MAS observations by demonstrating, for the first time, that WB/VAW is associated with an increased risk of COPD in adulthood. The older age of follow-up in WHEASE-2014 (mean 61 yr) compared with MAS (mean age 51 yr), the greater number of subjects, in particular control subjects, with FEV_1 data at this age in WHEASE-2014 (329 subjects with 239 control subjects) compared with MAS (197 subjects with 48 control subjects) might have contributed to our detecting a modest increased COPD risk among subjects with WB/VAW. Follow-up of the British 1958 (29) birth cohort also reported that childhood wheezing illness was not associated with an increased rate of FEV_1 decline in adults between 35 and 45 years of age, although the age of follow-up was somewhat younger than that in WHEASE-2014 or MAS.

The present study and MAS gave important insights into the natural history of obstructed lung function from childhood to later life. The first insight of a link between respiratory outcomes in early and later life came from the observation of correlations between mortality rates from infant and adult respiratory causes within geographic areas (30). Tracking of suboptimal ventilatory function was demonstrated in the Tucson cohort, in which reduced ventilatory function at 2.3 months was associated with a reduced FEV_1/FVC ratio and reduced FEV_1 up to age 22 years (12). A study of similar design in Australia also observed associations between reduced ventilatory function at 1 month and reduced ventilatory function in 18 year olds (13). These studies suggest that early life factors program airway development, such that reduced ventilatory function is established very early in the life course and tracks up to the age of 22 years. The positive association between fetal size at 10 weeks' gestation and FEV_1 in 10 year olds suggests that the factors determining lung function trajectory are already active at a very early developmental stage (31). A consequence of such tracking is that infants and children with reduced ventilatory function would be more likely to have the same reduced FEV_1/FVC ratio as adults. Although WHEASE and other studies have demonstrated that this is the case for CA, WHEASE has now confirmed that childhood WB/VAW is also associated with an increased risk of COPD in later life. Although we were not able to compare childhood lung function between subjects with WB and control subjects, our findings suggest that lung function among those with WB was not obviously abnormal in childhood, when standardized to a modern reference population, but during adulthood those with WB were at increased risk of obstructed lung function, independent of confounders. Our observations support the paradigm that CA is linked to COPD by an airway developmental abnormality present from childhood. However, the association between WB and COPD may be by a different mechanism that affects the airways, or by the same mechanism but which is of lesser magnitude and/or acting later in life.

Table 3. Ventilatory Function Characteristics in WHEASE 2014 by 1964 and 2001 Wheezing Phenotype Categories

		1964 Definitions				2001 Definitions (Including AOW)		
	Total (n = 330)*	CA† (*n = 38*)	WB/VAW‡ (*n = 53*)	Controls§ (*n = 239*)	*P* Value	AOW (*n = 57*)	Controls‖ (*n = 182*)	*P* Value
FEV_1, %pred, mean (95%CI)	95.5 (93.4–97.3)	81.3 (72.8–89.9)	97.3 (93.2–101.4)	97.1 (95.1–99.2)	<0.001¶	92.5 (88.0–97.0)	98.6 (96.3–101)	<0.001¶
FVC, %pred, mean (95%CI)	107 (106–109)	100 (94.4–106)	108 (104–112)	108 (106–110)	0.014¶	107 (102–112)	108 (106–110)	0.025¶
$FEF_{25–75\%}$,%pred, mean (95%CI)	76.1 (72.2–79.9)	55.9 (43.7–68.1)	83.1 (72.4–93.8)	77.8 (73.5–82.1)	0.001¶	67.3 (59.1–75.5)	81.1 (76.1–86.1)	<0.001¶
FEV_1/FVC, mean (95%CI)	0.69 (0.68–0.70)	0.62 (0.58–0.66)	0.71 (0.68–0.73)	0.70 (0.69–0.71)	<0.001¶	0.68 (0.66–0.70)	0.71 (0.70–0.73)	<0.001¶
FEV_1/FVC < 0.7, n (%)	143 (43.3)	27 (71.1)	23 (43.4)	93 (38.9)	0.001**	29 (50.9)	64 (35.2)	<0.001**
FEV_1/FVC < LLN, n (%)	100 (30.3)	23 (60.5)	14 (26.4)	63 (26.4)	<0.001**	21 (36.8)	37 (20.3)	<0.001**

Definition of abbreviations: %pred = percentage predicted; AOW = adult-onset wheeze; CI = confidence interval; LLN = lower 95% confidence limit of the internationally agreed predictive equations for normality; WB/VBW = wheezy bronchitis/virus-associated wheeze; WHEASE = What Happens Eventually to Asthmatic children: Sociologically and Epidemiologically.
*Questionnaire data in 328 subjects and physiological measurements in 329 subjects.
†Childhood asthma.
‡Childhood WB/VAW.
§Childhood controls.
‖Adult controls. When applying the 2001 definitions, spirometry at ages 60 to 65 years is compared only between individuals with AOW (i.e., who were defined as controls in 1964) and subjects who never developed respiratory symptoms.
¶Difference across childhood groups: one-way analysis of variance.
**Difference across childhood groups: χ^2.

Although the initial assessment of cohort members took place at age 10 to 15 years, there is reliable evidence of very early onset of symptoms among those with CA, whom we described as already having reduced FEV_1 as children and being at highest risk for COPD at ages 60 to 65 years. As part of the initial assessment of this cohort, the primary and secondary care medical notes of the subset with CA were examined, and 44% had onset of symptoms by 2 years of age and 81% by 5 years of age (18). Therefore, we can be confident in the age at onset of symptoms in those with CA. Although we are confident that the clinical assessment of the children with wheezy bronchitis was just as thorough, because of the asthma focus of the original study, the age of onset of wheezy bronchitis was not published. Despite clinical diligence, it is possible that some subjects with AOW may have had a history of transient wheeze in early childhood that was not reported or recalled by parents when their child was aged 10 to 15 years; this phenomenon has been previously described (12). Such misclassification of children who wheezed as "controls" is a null bias likely to attenuate any association between WB/VAW and COPD. When subjects with AOW are removed from the childhood control group, there is a marginal increase in risk for COPD among those with wheezy bronchitis (Table 5), but there is no difference in change in lung function (Table 6). This suggests that unreported latent/transient childhood wheeze that recurred in later life has not substantially affected our results. This was not a birth cohort study, and our study design, in which symptom status is unknown for early childhood (except the CA group), may lead to misclassification of phenotypes. This is a weakness that we acknowledge. However, misclassification of WB/VAW children as control subjects is likely to attenuate any association between WB/VAW and COPD (i.e., a null bias).

In WHEASE-1995, 177 (11.5%) of 1542 control subjects had developed wheeze between 16 to 46 years of age (17). In the present study, these subjects with AOW had an increased risk of developing

Table 4. Associations between 1964 and 2001 Wheezing Groups and Chronic Obstructive Pulmonary Disease at Ages 60 to 65 Years: Results of Logistic Regression Analysis

	FEV_1/FVC < 0.7 [*Adjusted OR* (95% CI)*]	FEV_1/FVC < LLN [*Adjusted OR* (95% CI)*]
1964 wheeze groups		
Childhood controls, n = 239	1.00	1.00
Childhood asthma, n = 38	4.39 (1.98–9.73)	5.29 (2.46–11.4)
Childhood WB/VAW, n = 53	1.36 (0.71–2.63)	1.39 (0.67–2.89)
2001 wheeze groups		
Childhood controls, n = 182	1.00	1.00
Childhood asthma, n =38	4.90 (2.18–11.0)	6.42 (2.90–14.2)
Childhood WB/VAW, n = 53	1.52 (0.77–2.99)	1.67 (0.79–3.60)
Adult-onset wheeze (16–45 yr), n = 57	1.56 (0.82–2.96)	1.97 (1.00–3.91)

Definition of abbreviations: CI = confidence interval; OR = odds ratio; LLN = lower 95% confidence limit of the internationally agreed predictive equations for normality; WB/VBW = wheezy bronchitis/virus-associated wheeze.
*Adjusted for sex, age, history of ever smoking, and Scottish Index of Multiple Deprivation in 2014.

Table 5. Associations between 1964 and 2001 Wheezing Groups and Chronic Obstructive Pulmonary Disease at Ages 35 to 65 Years: Discrete Time Logistic Model Using All Data Collected between 1989 and 2014

	$FEV_1/FVC < 0.7$ [*Adjusted OR* (95% CI)*]	$FEV_1/FVC <$ LLN [*Adjusted OR* (95% CI)*]
1964 wheeze groups		
Childhood controls, n = 820	1.00	1.00
Childhood asthma, n = 135	5.79 (3.44–9.73)	5.68 (3.41–9.44)
Childhood WB/VAW, n = 189	1.65 (1.04–2.61)	1.56 (0.94–2.59)
2001 wheeze groups		
Childhood controls, n = 637	1.00	1.00
Childhood asthma, n = 135	6.37 (3.73– 10.9)	5.11 (2.93–8.92)
Childhood WB/VAW, n = 189	1.81 (1.12–2.91)	1.48 (0.86–2.57)
Adult-onset wheeze (16–45 yr), n = 183	1.45 (0.91–2.32)	1.86 (1.11–3.13)

Definition of abbreviations: CI = confidence interval; LLN = lower 95% confidence limit of the internationally agreed predictive equations for normality; OR = odds ratio; WB/VBW = wheezy bronchitis/virus-associated wheeze.
*Adjusted for sex, age, history of ever smoking, and Scottish Index of Multiple Deprivation in 2014.

COPD. This was related to a more rapid decline in FEV_1 than control subjects and was not due to having previously lower FEV_1, which suggested that extrinsic environmental or occupational factors may play an important role.

The strengths and limitations of the present study are a consequence of the design and focus of previous WHEASE phases. As an unselected community-based cohort, the study provides widely generalizable results. Although the 50-year follow-up is the same as MAS, our age of follow-up has been the oldest of any study to date, with participants being 10 years older than those in MAS. Clinical assessment of the children at age 10 to 15 years by an experienced pediatrician. complemented with spirometry and review of medical notes in symptomatic subjects instead of total reliance on questionnaire responses is another strength. The main limitation of the present study is the restriction of sample size by historical precedent. The power to detect an association between WB/VAW and COPD was based on WHEASE 2001, and although we exceeded the follow-up target, *post hoc* analysis demonstrated that the study was underpowered to detect an association between WB/VAW and COPD in WHEASE-2014 data, because the prevalence of $FEV_1/FVC < 0.7$ in the control group was 35% and not 12%, as in WHEASE-2001 (19). Participant assessment in WHEASE-2014 was identical to previous phases of WHEASE, except for spirometry, which was conducted post-bronchodilator. Previous WHEASE studies could have overestimated the prevalence of $FEV_1/FVC < 0.7$; however, this does not appear to have been the case, because comparison of WHEASE-2001 and -2014 demonstrated that although 20% of participants transitioned from $FEV_1/FVC \geq 0.7$ to $FEV_1/FVC < 0.7$, only 2% changed from $FEV_1/FVC < 0.7$ to $FEV_1/FVC \geq 0.7$. Fifty-eight percent of those invited to participate had spirometric assessment as part of the most recent assessment of this cohort, and it is highly unlikely that incomplete participation introduced selection bias that might create a false positive findings, because we demonstrated that, with the exception of under-representation of smokers, the participants were similar to nonparticipants. Because of the association between smoking and respiratory morbidity, this will diminish and not exaggerate the associations reported herein.

This is the first study to follow children with wheeze into their seventh decade. Childhood WB/VAW increased the risk of COPD and was associated with reduced FEV_1 evident by the fifth decade. Previous studies suggest that this occurs very early in life, possibly in utero. This has implications for the long-term management of children who develop WB/VAW. We have also confirmed that CA is associated with an increased risk of COPD and shown that AOW results in more rapid decline in ventilatory function. ■

Table 6. Linear Mixed-Effects Modeling Applied to all FEV_1 Data Collected between 1989 and 2014, Estimates of Group Difference in FEV_1 Based on 1964 and 2001 Classifications

	FEV_1	
	Estimate* (95% CI)	***P* Value**
1964 wheeze groups		
Overall: childhood controls vs. CA, L	−0.56 (−0.72 to −0.40)	<0.001
Overall: childhood controls vs. WB/VAW, L	−0.19 (−0.32 to −0.05)	0.008
Difference in decline: childhood control vs. CA, L/yr	0.0001 (−0.005 to 0.007)	0.726
Difference in decline: childhood control vs. WB/VAW, L/yr	0.002 (−0.003 to 0.007)	0.453
2001 wheeze groups		
Overall: childhood controls vs. CA, L	−0.56 (−0.72 to −0.40)	<0.001
Overall: childhood controls vs. WB/VAW, L	−0.18 (−0.32 to −0.04)	0.028
Overall: childhood controls vs. AOW, L	−0.04 (−0.11 to 0.20)	0.573
Difference in decline: childhood controls vs. CA, L/yr	−0.0008 (−0.007 to 0.007)	0.817
Difference in decline: childhood control vs. WB/VAW, L/yr	0.0002 (−0.005 to 0.006)	0.935
Difference in decline: childhood control vs. AOW, L/yr	−0.009 (−0.016 to −0.002)	0.008

Definition of abbreviations: AOW = adult-onset wheeze; CA = childhood asthma; CI = confidence interval; WB/VBW = wheezy bronchitis/virus-associated wheeze.
n = 1,144 records analyzed.
*Adjusted for sex, age, history of ever smoking, and Scottish Index of Multiple Deprivation in 2014.

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